SUMMARY BASIS FOR APPROVAL

PLA: # 95-0979

ELA: # 95-0975

Manufacturer:
Biogen, Inc.
14 Cambridge Center
Cambridge, MA 02142

Drug License Name:
Interferon beta-1a

Drug Trade Name:
AVONEX™

I. INDICATION FOR USE

Interferon beta-1a (AVONEX™) is indicated for the treatment of relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Safety and efficacy in patients with chronic progressive multiple sclerosis have not been evaluated.

II. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

Interferon beta-1a is supplied as a lyophilized powder in a single-use vial containing 33 mcg (6.6 million IU) of Interferon beta-1a, 16.5 mg Albumin Human, USP, 6.4 mg Sodium Chloride, USP, 6.3 mg Dibasic Sodium Phosphate, USP, and 1.3 mg Monobasic Sodium Phosphate, USP, and is preservative-free (approximate pH 7.3). Diluent is supplied in a 10 ml single-use vial (Sterile Water for Injection, USP, preservative-free).

The recommended dosage of Interferon beta-1a for the treatment of relapsing forms of multiple sclerosis is 30 mcg injected intramuscularly once a week (1.0 ml of reconstituted material). Interferon beta-1a is intended for use under the guidance and supervision of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in intramuscular injection technique.

III. MANUFACTURING AND CONTROLS

A. Background

Interferon beta-1a is produced by recombinant DNA technology in chinese hamster ovary (CHO) cells. The amino acid sequence of the recombinant protein produced by these cells is identical to naturally occurring interferon beta and has thus been given the designation 1a. Interferon beta-1a

is a single chain, glycosylated polypeptide 166 amino acid residues in length, and with an approximate molecular weight of 22.5 kD. The product (BG9015) used in the Phase 3 clinical trial that supports licensure was manufactured by a company called Bioferon in Germany which was a 50/50 joint venture between Biogen in Cambridge, MA and Rentschler Biotechnology in Laupheim, Germany. Data on BG9015, manufactured by Bioferon, were submitted by Biogen in a master file. The pivotal phase 3 trial was conducted under an investigator initiated IND which cross referenced the Biogen master file. During the trial, Bioferon went into receivership and there was no further production of BG9015. There was, however, enough BG9015 vialed final product to finish the pivotal trial.

Biogen developed a new CHO cell line that carried the interferon beta gene and began production of product referred to as BG9216. These CHO cells were adapted for suspension culture. Data supporting the use of this cell line were submitted to CBER and showed that the specific activity of BG9216 was somewhat greater than BG9015, and that it contained an additional peak in the peptide map. This additional peak was characterized and at [redacted] In addition, pharmacokinetic bioequivalence studies in humans showed that BG9216 was not equivalent to BG9015. Based on the biochemical and pharmacokinetic differences, Biogen was informed that BG9216 was not comparable to BG9015.

Biogen developed another Interferon beta-1a cell line, and the product produced by this cell line was designated BG9418. BG9418 has been extensively characterized and compared in side-by-side analyses with BG9015 (see detailed discussion below). Biological, biochemical, and biophysical analyses have shown that the two molecules are comparable. Biological activities of each molecule are similar using several different assays, such as anti-viral, anti-proliferation, and enhancement of MHC class I expression. Peptide maps as determined by high pressure liquid chromatography of peptides derived by proteolysis of the two proteins are superimposable. Carbohydrate analysis revealed a similar pattern of major oligosaccharide forms on each protein. Finally, pharmacokinetic studies in humans using the two molecules revealed a pattern of clearance from the blood that was determined to be equivalent by rigorous statistical analyses (see detailed discussion under Pharmacology). For these reasons the Agency has determined that BG9015 and BG9418 are comparable and that clinical data derived from the use of BG9015 can support the licensure of the BG9418 molecule.

B. Comparative Analysis of BG9015 and BG9418

The production and purification process for BG9015 and BG9418 differ slightly. The CHO cell line for BG9418 grows in suspension whereas the CHO cell line for BG9015 grows as an adherent culture. Additional differences occur in the extraction method and column chromatography purification procedures. Comparative biochemical analyses consist of both historical data supplied in the original master file and side-by-side analyses of drug product from which albumin (15 mg/ml) was removed when necessary to facilitate side-by-side comparative analyses.

Peptide map: The primary amino acid sequence is identical between BG9015 and BG9418. The peptide map for BG9418 was compared to BG9015 historical controls and in a side-by-side analysis. The peptides eluted in a similar manner with respect to elution times and peak height for the two preparations. Peptides produced from BG9015 and BG9418 were sequenced by Edman degradation and the sequence of all the peptides for both products corresponded to the natural sequence.

N-terminal amino acid sequencing: N-terminal amino acid sequencing of up to 15 amino acids revealed that the predominant species in both BG9015 and BG9418 was the predicted N-terminal sequence. A minor form of Interferon beta-1a (des-1), characterized by the lack of the N-terminal methionine, was detected in both preparations. A quantitative difference was found in the level of des-1 in BG9418 and BG9015. However, the biological activity of the des-1 containing material is identical to material containing the N-terminal methionine. Moreover, CD spectra for the two molecules are superimposable and intrachain disulfide bonding is the same. There was no evidence for C terminal heterogeneity in either BG9015 or BG9418. BIAcore analysis of BG9015 and BG9418 using an antibody that recognizes only structurally intact interferon beta was virtually identical for the two molecules.

Carbohydrate analysis: Carbohydrate analysis was done on both BG9015 and BG9418, using fluorescence assisted carbohydrate electrophoresis and mass spectometry. Three major glycoforms were detected and the proportions of each were essentially identical for both BG9418 and BG9015. Some differences were detected in the minor glycoforms between the two products, but they did not contribute to any detectable difference in the pharmocokinetics in humans. Therefore, the carbohydrate fingerprint for those glycoforms comprising the majority of the product was comparable between the two preparations.

Immunoblotting analyses: Immunoblotting analyses were performed on formulated BG9015 and BG9418. Immunoblots revealed one major band and two minor bands for both products. Although there was more of one of the minor bands in BG9418 compared to BG9015, this had no effect on the overall specific activity of the BG9418 product. All three bands were Interferon beta-1a. Immunoblots of the IEF gels of formulated product showed some differences. Most of the differences observed on the blot were the result of the des-1 species which has the same bioactivity as the molecule with the intact methionine.

Reverse phase HPLC: Both BG9015 and BG9418 revealed identical elution times on reverse phase HPLC when studied in a side-by-side analysis. Deamidated product was noted in both preparations. While a quantitative difference was found in the level of deamidated product in BG9418 and BG9015, the bioactivity of the deamidated product was identical to that of the unmodified product.

Receptor binding and other functional assays: Studies with BG9015 and BG9418 were done side-by-side in receptor binding competition assays and bioactivity assays assessing different actions of the Interferon beta-1a molecule. Competition curves were identical for both BG9015

and BG9418 in their ability to inhibit BG9418 binding. Antiviral activity of the drug substance was virtually identical and within the variability of the assay. Bioactivity as measured by antiproliferation and induction of MHC class I expression was also identical for the two preparations.

Conclusion: The biological, biochemical, and biophysical data support the ability of BG9418 to substitute for BG9015. In addition, human pharmacokinetic studies have demonstrated that BG9015 is comparable to BG9418 (see Pharmacology section). Based on these findings, BG9418 is comparable to BG9015 and the clinical data generated using BG9015 will support the licensure of BG9418.

C. Manufacturing and Controls for BG9418

The human interferon beta gene was cloned by PCR from human genomic DNA isolated from a human leukocyte cell line. A CHO cell line was used to generate the final cell line which expresses the interferon beta gene. The parental cells, the MCB, the MWCB and post production cell banks were all characterized for stability, karyology, isoenzymes, nucleic acid analysis, scanning EM, mouse antibody production, hamster antibody production, mycoplasma, adventitious viruses, retroviruses, transmission EM of conditioned media, sterility and viability after thaw. All of the above assays demonstrated that there was no change in the character of the cell line as a result of its being expanded to large scale culture. All tests for the presence of infectious agents were negative except for intracytoplasmic A-type retrovirus-like particles which are well described in CHO cells. The mRNA encoding interferon beta was also sequenced in post production cells and shown to be identical to the sequence of the human interferon beta gene.

Manufacture of the bulk intermediate is performed at Biogen, Inc. Cambridge, MA. Interferon beta-1a is secreted by CHO cells in culture. Following fermentation, cells and cell free debris are removed, and the product is purified by a series of chromatographic steps. A viral inactivation step is performed. The purified product is filtered, bottled, and stored as bulk intermediate. Product release tests and specifications for the bulk intermediate are appended.

Formulation and filling is carried out at [redacted]. Frozen bulk is shipped from Biogen to [redacted] on dry ice in shipping containers. Bulk intermediate is formulated with HSA and diluent and filtered sterilized. Vials are filled, lyophilized and sealed. Product release testing and specifications for the final product are appended.

D. Stability

Bulk Intermediate: The dating period for the Interferon beta-1a bulk intermediate is 12 months from the date of filling the bulk intermediate containers. To support this dating period, Biogen submitted 12 months of stability data on three commercial-scale batches of bulk intermediate which were studied at three different temperatures. Testing for evaluating bulk intermediate stability included: appearance, protein concentration, potency/specific activity, SDS-PAGE

reducing gel (coomassie blue stain), size exclusion chromatography (for aggregates), peptide map, particulates (HIAC), and endotoxin (LAL). Sterility is not determined because the bulk is sterile filtered before filling. The purified bulk is tested for bioburden at the time of release. The proposed test methods for monitoring stability of the bulk intermediate appear suitable.

Hold points in the purification process include storage of column eluates. Data supporting these hold points in the purification process were provided.

Drug Product: Bulk intermediate is shipped from Biogen to [redacted] The dating period for the finished product is 15 months from the date of final sterile filtration of the formulated bulk when stored at 2-8° C.

Biogen submitted 15 months of stability data on three lots and 12 months of stability data on three additional lots of interferon beta-1a finished product. Finished product stored for up to 12 months at 2-8° C was also assessed for stability following reconstitution in sterile water for injection. Reconstituted product was evaluated for stability following storage upright and inverted at 2-8° C for 24 hours. Testing on the finished product includes: appearance, pH, interferon beta-1a content by ELISA, potency (antiviral assay), residual moisture, particulates (HIAC), sterility, endotoxin (LAL).

Additional supportive data for stability of the BG9418 finished product included an accelerated degradation study on the finished product stored for up to 9 months at 25° C and 40° C, and 30 months of real time stability at 2-8° C on three lots of BG9015 finished product.

E. Validation

The processes, procedures, and equipment used to manufacture Interferon beta-1a have been validated to provide assurance that they operate in a reproducible manner and will produce consistent product. Appropriate specifications for environmental monitoring during the critical steps of manufacture have been established. Five consecutive batches of BG9418 bulk intermediate (drug substance) were manufactured, and the full-scale production process validated through compilation of process results. Similarly, three consecutive batches of BG9418 final drug product were manufactured and the production process validated. The results show that all batches were consistently manufactured and validated for removal of DNA, cell culture medium additives, and process reagents, and for viral inactivation and removal.

F. Labeling

The labeling, including the package insert, the package label, and the container label, have been reviewed and found to be in compliance with 21 CFR 610.60, 610.61, 610.62, 201.56, and 201.57. The tradename AVONEX™ is not known to be in conflict with that of any other approved product.

G. Establishment Inspection

A prelicensing inspection was performed at Biogen's manufacturing facility in Cambridge, MA on February 5-9, 1996 and the facility was found to be in compliance with current good manufacturing practices. An inspection of [redacted] was performed between February 20 and March 12, 1996. This contract facility does formulation, filling and lyophilization and was found to be in compliance with current good manufacturing practices. Compliance status checks were done on the following additional contract manufacturing facilities: [redacted] (for labeling and packaging); and [redacted] These contract facilities were in compliance with current good manufacturing practices.

H. Environmental Impact

An Environmental Impact Analysis Report was submitted by Biogen as part of the establishment license application. All applicable federal, state and local environmental regulations are observed.

IV. PHARMACOLOGY

A. Background

Interferons are a family of naturally occurring proteins and glycoproteins termed cytokines. They are produced by eukaryotic cells in response to viral infection and other biological inducers and mediate antiviral, antiproliferative and immunomodulatory activities. Three major interferons have been distinguished: alpha, beta, and gamma. Interferons alpha and beta form the Type I class of interferons, and interferon gamma is a Type II interferon. These interferons have overlapping but clearly distinct biological activities.

Interferon beta is one member of the Type I family, and is produced by various cell types including fibroblasts and macrophages. Interferon beta exerts its biological effects by binding to specific receptors on the surface of human cells. This binding initiates a complex cascade of intracellular events that leads to the expression of numerous interferon-induced gene products and markers. These include 2', 5'-oligoadenylate synthetase (2', 5'-OAS), neopterin, Class I major histocompatibility antigen and β2-microglobulin. Several of these markers have been used to monitor the biological activity of interferon beta-1a in treated monkeys, in normal subjects and in MS patients.

The specific mechanism by which Interferon beta-1a exerts its effects in MS has not been defined. There is no *in vitro* model for MS and no generally accepted animal model of MS in a species that is pharmacologically responsive to Interferon beta-1a. The activities of Interferon beta-1a are highly species specific, and the most pertinent pharmacologic information is derived from studies in human cells in culture, in humans, and, to a lesser extent, in rhesus monkeys.

The clinical investigation of Interferon-beta 1a has utilized 4 closely related versions which are designated BG9014, BG9015, BG9216, BG9418. BG9014 and BG9015 were produced from the same CHO cell line; whereas, BG9216 and BG9418 were from different CHO cell lines. BG9015 and BG9014 differed in their respective purification processes. The amino acid sequences of BG9014, BG9015, and BG9418 were identical to natural human interferon-beta, however, BG9216 demonstrated structural differences. The carbohydrate structures of all four materials were similar to natural human interferon-beta. Bioequivalence studies demonstrated that BG9015 was pharmacokinetically equivalent to BG9418 but not to BG9216. BG9015, made by an affiliate of Biogen, was used in most of the clinical trials including pivotal studies of multiple sclerosis, but is no longer available. BG9216 was used in preclinical toxicity and phase 1 studies, but development of BG9216 was stopped after it was found to be pharmacokinetically different from BG9015. Version BG9418 was shown to be equivalent to BG9015 in pharmacokinetic studies in normal human volunteers, and is the commercial version of the product.

B. Pharmacokinetic Comparability Study

Study Design: A double-blind, randomized, 2-way cross-over study was conducted using healthy male and female volunteers. The pharmacokinetic profiles of BG9015 and BG9418 were compared at a dose of 75 microgm after IM injection. Serum levels of drug were assayed to determine pharmacokinetic equivalence in 30 subjects using an anti-viral bioassay. To determine pharmacokinetic equivalence, AUC (U-h/ml) was selected to be the primary endpoint. Cmax (U/ml) and Tmax (h) were also determined, but considered to be secondary or supporting endpoints. Because of the pharmacodynamic nature of the analytical assay, pharmacokinetic bioequivalence was determined using both parametric and non-parametric procedures (Wilcoxon-Mann-Whitney). In addition, a re-sampling or bootstrap technique was used for statistical comparisons.

Results: For BG9015 vs BG9418 the following pharmacokinetic values were computed: AUC (U-h/ml) - 1997 vs 2242; Cmax (U/ml) - 96 vs 103; Tmax (h) - 13 vs 13. As reported in the PLA with a convention for non-quantifiable plasma levels, the bioequivalence of BG9418 relative to BG9015 in a parametric test for the ratio of AUCs was 100.2% to 125.8% for a 90% confidence interval (CI) with a mean of 112.3% when all subjects' results were analyzed. With the exclusion of an apparent outlier the CI of the ratio of the AUCs was 97.9% to 119.1% with a mean of 110%. The decision to consider subject 106's data an outlier was based on the AUC ratio (BG9418/BG9015) of 316 which greatly exceeded the range for the remaining subjects. With the exclusion of the outlier the CI was 91 to 123%. After assigning all serum antiviral activities that were below quantifiable limits to zero, the bioequivalence based on AUC was 100.6% to 127.2% with a mean of 113.1%.

Because of the non-normality of the data, a non-parametric method was used to establish pharmacokinetic equivalence. When the non-parametric method was used with a ±20 rule and two one-sided tests conducted at the 5% level, the procedure yielded results indicating pharmacokinetic bioequivalence between the 2 versions. When bioequivalence was computed

based on AUC values with the convention of assigning serum levels to some selected and unmeasurable levels, the upper (U) and lower (L) endpoints were found to be within acceptable limits (W^{L} =187> w(0.95) = 143 and W_U = 63 < w(0.05) =67). For nonparametric calculations without usage of the convention, bioequivalence was observed (W_L = 186 > w(0.95) = 143 and W_U = 62 < w(0.05) = 67).

Based on Cmax, the pharmacokinetic bioequivalence of BG9418 relative to BG9015 was 107.5% with a CI of 93.3% to 123.9%. No values were excluded in computing Cmax for equivalency. An ANOVA was performed to assess the influence of period, sequence, and carry-over effect; no period or sequence effects were found.

In addition to the parametric and nonparametric methods, a resampling or bootstrap technique was applied to the data for the purpose of determining bioequivalence. Using the AUC values for BG9015 and BG9418, the median and 90% CI was computed. Confidence intervals with and without an apparent outlier were determined. Primarily based on AUC and secondarily on Cmax, BG9015 and BG9418 are considered pharmacokinetically bioequivalent.

Pharmacodynamic markers of neopterin and beta2-microglobulin were used in an analysis similar to that for the pharmacokinetic endpoint of AUC. The ratio of the CI for neopterin's AUC was 99.0% to 156.3% with a mean of 124.4%; beta2-microglobulin was 95.6% to 167.6% with a mean of 126.6%. Males experienced significantly higher AUCs levels than females for both neopterin and beta2-microglobulin, which was statistically significant for beta2-microglobulin ($P<0.001$). Other endpoints for the pharmacodynamic measures were obtained (Tmax, maximal value, and induction ratio of peak to baseline). In the analysis of pharmacodynamic data, a number of subjects or their individual values were excluded from the analysis. Exclusion of data points or subjects varied by the pharmacodynamic marker being measured, and therefore, was not consistent across markers.

C. Clinical Pharmacology

Measurements of pharmacodynamic markers were collected during the clinical pharmacology program. Data on three markers were obtained: beta2-microglobulin, neopterin, and 2',5'-oligoadenylate synthetase. Interferon beta-1a increased the expression of MHC class I and associated proteins such as beta2-microglobulin. Neopterin is a product of macrophages and T cells and reflects their activation. 2',5'-oligoadenylate synthetase is an enzyme which is induced by Interferon beta-1a and is involved in viral suppression. In both clinical and preclinical studies, induction of the biological response markers roughly correlated with serum activity levels of interferon.

Pharmacokinetic endpoints were responsive to increased dose as were biomarkers. Dose proportionality was observed with the SC route of administration. Beta2-microglobulin levels increased linearly with log dose of BG9015. Serum levels of interferon-beta were measured

through the use of an antiviral assay. The following pharmacokinetic endpoints were determined: observed Cmax, observed Tmax, and AUC as calculated by the trapezoidal rule. Furthermore, the elimination t1/2 was estimated by a regression technique. These estimates are subject to significant variability due to the assay methodology.

After intravenous administration, the initial t1/2 appears to be approximately 4 minutes and the terminal t1/2 is 3.5 to 4.0 h as measured by an antiviral assay. Peak serum activity was achieved in the following order by route of administration: IV > IM > SC. Bioavailability of a SC administered dose appears to be less than after IM. However, pharmacokinetic studies for bioavailability, as well as the pharmacokinetic endpoint of volume of distribution, are probably not accurate due to an underestimation of systemic exposure after IV dosing.

Following injection of Interferon-beta 1a by IV, IM, SC a persistent biological response (defined as increases in beta2-microglobulin, neopterin, and 2',5'-oligoadenylate synthetase) was observed. Biological response markers generally peaked 48 h after administering a IM or SC dose; after an IV injection biological markers peaked at approximately 24 h post dose. Overall systemic exposure as measured by AUC appeared to correlate with neopterin induction. Intramuscular injection appeared to induce higher levels of biological response markers than SC or IV injections. Generally, the onset of pharmacodynamic effects were delayed and of greater duration when compared to pharmacokinetic effects.

D. Preclinical Pharmacology and Toxicology

Test materials utilized in preclinical safety evaluation included three closely related forms of Interferon beta-1a: BG9015, the product used in the pivotal phase 3 study; BG9418, the product intended for commercialization; and BG9216 which contained a mixture of two forms of Interferon beta-1a. The safety, biochemical, and pharmacologic activity of Interferon beta-1a, derived from CHO cells were evaluated in mice, guinea pigs, and Rhesus monkeys *in vivo*, and in peripheral blood leukocytes derived from humans, mice, rats, rabbits, dogs, guinea pigs, Rhesus and cynomolgus monkeys, and woodchucks *in vitro*. In *in vitro* pharmacodynamic assays, only PBL from Rhesus monkeys were found to exhibit a dose-related increase in 2',5'-OAS activity similar to that observed with human cells; a lesser dose-related increase in 2',5'-OAS was also observed when PBL from woodchucks were incubated with IFNB-1a *in vitro*. Because of the species specificity in the pharmacodynamic response, *in vivo* pharmacologic, pharmacokinetic, and repeat-dose toxicology testing was conducted in the Rhesus monkey. Pharmacokinetic studies in this species demonstrated similar absorption and elimination profiles after either s/c or i/m injection, with an approximate t½ elim of 4 to 6 h. Systemic exposure, as calculated from the AUC from time zero to 24 h was increased in a dose-related fashion, was approximately linear, and was similar for both the i/m and s/c routes. Bioavailability by either route was approximately 100%. Interferon beta-1a has pharmacologic and toxicologic profiles similar to other type I interferons; major findings in Rhesus monkeys after repeated s/c dosing at 0.1, 0.25, 1 or 10 MU/kg (0.3, 1.25, 5, or 50 µg/kg) of Interferon beta- 1a included fever, decreased food consumption and weight loss, slight decreases in platelet and leukocyte counts, enlargement of

regional (inguinal, iliac, axillary) lymph nodes, and local irritation and inflammation at the site of injection. The decrease in platelets and food consumption, and the fever were related to the dose of Interferon beta-1a administered, and were only evident during the first two weeks of treatment. All changes were reversible during a 28 d recovery period, with the exception of the lymphadenopathies. Histologically, increases in lymphoid hyperplasia, chonic inflammation, and hemorrhage at the injection site were observed after 14 to 28 d of treatment, and were incompletely resolved after 28 d recovery. The no observable adverse effect level (NOAEL) for Interferon beta-1a in the Rhesus monkey was 0.25 MU (1.25 μg)/kg, administered every other day for 14 d. Induction of pharmacodynamic markers of interferon activity, including 2 to 50-fold increases in serum neopterin and 2',5'-OAS levels were observed in animals intitially, but declined after treatment for more than 13 days. These levels returned to baseline after a 28 d recovery period. A loss of detectable Interferon beta-1a activity in the serum and development of neutralizing antibody activity were noted at the end of treatment period in all studies, and antibody titers continued to increase during the recovery phase.

BG9216 was used for the reproductive and developmental toxicity studies in female Rhesus monkeys. This product was found to inhibit ovulation and decrease serum progesterone in normally cycling female monkeys, and had abortifacient effects in 2/10 monkeys when administered at 10 MU/kg (33 μg/kg) from days 21-50 of pregnancy. The NOAEL for toxicity to reproduction was 0.25 MU (0.8 μg)/kg, administered every other day for 30 days. This dose level is approximately 2 fold greater than the recommended weekly dose of 30ug (6MU) in MS patients, when normalized by body surface area.

V. MEDICAL

A. Background

Multiple sclerosis (MS) is one of the most important neurologic diseases due to its frequency, chronicity and severity. The onset is often in young adults. Most patients in the early stages have episodes of localized impairment related to focal disorders of the optic nerves, spinal cord, and brain white matter. These episodes often remit completely early in the disease. However, the episodes recur over a period of years. The localized neural disorder becomes widely scattered throughout the central nervous system white matter. The symptomatology includes motor weakness, paresthesias, impaired vision, diplopia and other disorders of gaze, tremor, ataxia, deep sensation losses, bowel and bladder dysfunction, and neuropsychiatric disorders. The period between the first symptom, often noted only retrospectively, and the more persistent and severe later episodes may be several years or longer. There are approximately 250,000 patients with MS in the United States, with annual incidence of approximately 9000.

The etiology of MS is unknown. However, MS is widely considered to be an autoimmune disease. The ongoing destruction of the CNS is due to immune system attack directed against the CNS myelin, but not peripheral myelin. Myelin basic protein (MBP), found in CNS myelin, is a putative agent in sustaining this autoimmune process. Most proposed therapies for MS are

attempts to modify the immune system's functions. Interferons are a family of molecules that exert both anti-viral and anti-proliferative activity on a variety of cell types. In addition, interferons have immunomodulatory activities that are dependent upon the type of interferon and the particular biological system studied.

In 1993 the FDA licensed an interferon beta for commercial sale in the US (Interferon beta-1b, Betaseron®, Chiron Corporation). A clinical trial with Betaseron showed efficacy in reducing the rate of exacerbations by approximately one third. It also had effects on the MRI lesion loads. The trial did not demonstrate efficacy with regard to slowing disability. As expected with an interferon, the side effects were considerable. Betaseron differs structurally from natural human interferon-beta; Betaseron is missing the amino terminus methionine, the cysteine at position 17 is replaced by a serine, and it is not glycosylated due to bacterial production methods. The specific activity of Betaseron is 32 MIU/mg, using an antiviral assay and the WHO recombinant human interferon beta standard. The licensed dose of Betaseron is 250μg SC qod. This dose equals 8MIU of the prior noted activity units, and is given 3½ times per week.

The Biogen product, Interferon beta-1a, retains the terminal methionine, has no substitutions, and is glycosylated. The specific activity of the Biogen product is approximately 200 MIU/mg, using an antiviral assay and the WHO natural interferon beta standard, Second International Human Fibroblast standard. The proposed dose is 30μg IM once per week, which equals 6 MIU of the noted standard.

B. Pilot Studies to Establish Dosing Regimen

Prior studies in multiple sclerosis patients with this product consist of two studies conducted on 5 patients to assess the tolerability and unblinding effects of several dose levels of this interferon. The two studies enrolled the same five patients. The two studies used products designated as BG9014 and BG9015. The two products were produced from the same cell line. BG9014 was the original product produced, and available at the time the clinical trial was being planned. Some changes in the manufacturing process were made by Bioferon, resulting in the new product designated BG9015. BG9015 was the product subsequently used in the phase 3 clinical trial.

The first study used BG9014 to assess the maximum dose of interferon that could be administered intramuscularly and not cause unblinding due to the interferon-associated symptoms. This study also examined whether acetaminophen or indomethacin performed better as a masking agent and compared levels of β_2-microglobulin at each dose. Patients received injections of 1.5, 3, 6, and 18 MIU of interferon with indomethacin as a masking agent, and 3,6, and 9.5 MIU of interferon with acetaminophen as a masking agent. The injections were given once per week, dispersed over a 14 week period, with 7 placebo injections randomly dispersed within the ordered 7 interferon injections. This study showed that β_2-microglobulin level increases were similar after 6 MIU and 9.5 MIU, and both were somewhat greater than after 3 MIU. The blinding assessment indicated that 6 MIU was the highest dose that could be given without unblinding by interferon-related symptoms occurring, and that both indomethacin and acetaminophen functioned similarly as

masking agents.

The second study used both the BG9014 and BG9015 products. The study was designed to provide assurance that there was no substantial change in the bioactivity of the new product, assessed by β_2-microglobulin levels. This study used a single injection of 6 MIU of BG9014 and 3, 6, and 12 MIU injections of BG9015. Each patient received all of the doses. This study showed that highly variable increases in β_2-microglobulin levels occurred after both the BG9014 and BG9015 products.

The conclusion from these two studies was that 6 MIU (30μg) of Interferon beta-1a was the dose selected for the phase 3 trial and acetaminophen was selected as the symptom masking agent.

C. Pivotal Study Design

The safety and efficacy of Interferon beta-1a in the treatment of relapsing MS was assessed in a multicenter, randomized, double-blind, placebo-controlled study. The stated primary objective of this study was to compare the time to the beginning of sustained progression of disability, as measured by the Expanded Disability Status Scale (EDSS), in patients with exacerbating multiple sclerosis (MS) between patients treated with Interferon beta-1a and those treated with placebo. Progression in disability was defined as an increase in the EDSS by 1.0 point from the baseline value which was maintained for at least 6 months as demonstrated by persistence of the increased EDSS at two consecutive six-monthly exams. This was intended to insure that purely transient increases associated with acute exacerbations did not contribute to the endpoint, and to account for the intra-rater variability of the EDSS assessment. This was called the Confirmed EDSS change.

The stated secondary endpoints were to determine if patients treated with interferon beta have

a) Less progression of disability as measured by extent of change in EDSS
b) Fewer on-study exacerbations
c) Longer time to first on-study exacerbation
d) Better functional status as measured by scales of physical, cognitive, and social disability
e) Fewer on-study courses of adrenocorticotropic hormone (ACTH) or corticosteroid treatments
f) Less upper extremity disability
g) Less lower extremity disability
h) Less overall worsening as assessed by the examining physician in a global assessment
i) Less increase in brain plaque load assessed by Gadolinium-enhanced MRI

The pivotal trial was a double-blind, randomized, placebo-controlled study, performed at four administrated study sites, with two treatment arms comprised of patients with relapsing multiple sclerosis (MS). Blinded treatments were administered by IM injection once per week for up to 2

years. Patients were not permitted to self-inject the study treatment, but rather were required to receive the weekly injections either at the study site or by a local health care professional. In this study, 301 patients received either 6 million IU (30 mcg) of Interferon beta-1a (n=158) or placebo (n=143) by IM injection once weekly. Patients were entered into the trial over a 2½ year period, received injections for up to 2 years, and continued to be followed until study completion. Two hundred eighty-two patients completed 1 year on study, and 172 patients completed 2 years on study.

Inclusion Criteria

- A diagnosis of definite MS of at least 1-year duration
- Either relapsing-remitting or relapsing-progressive disease
- At least two exacerbations in the 3 years prior to study entry, or one exacerbation per year if disease duration was less than 3 years. Exacerbations had to be documented by the medical record
- Exacerbation-free period of at least 2 months prior to study entry;
- Kurtzke EDSS between 1.0 and 3.5, inclusive (patients fully ambulatory at study entry)
- Male or Female, between the ages of 18 and 55

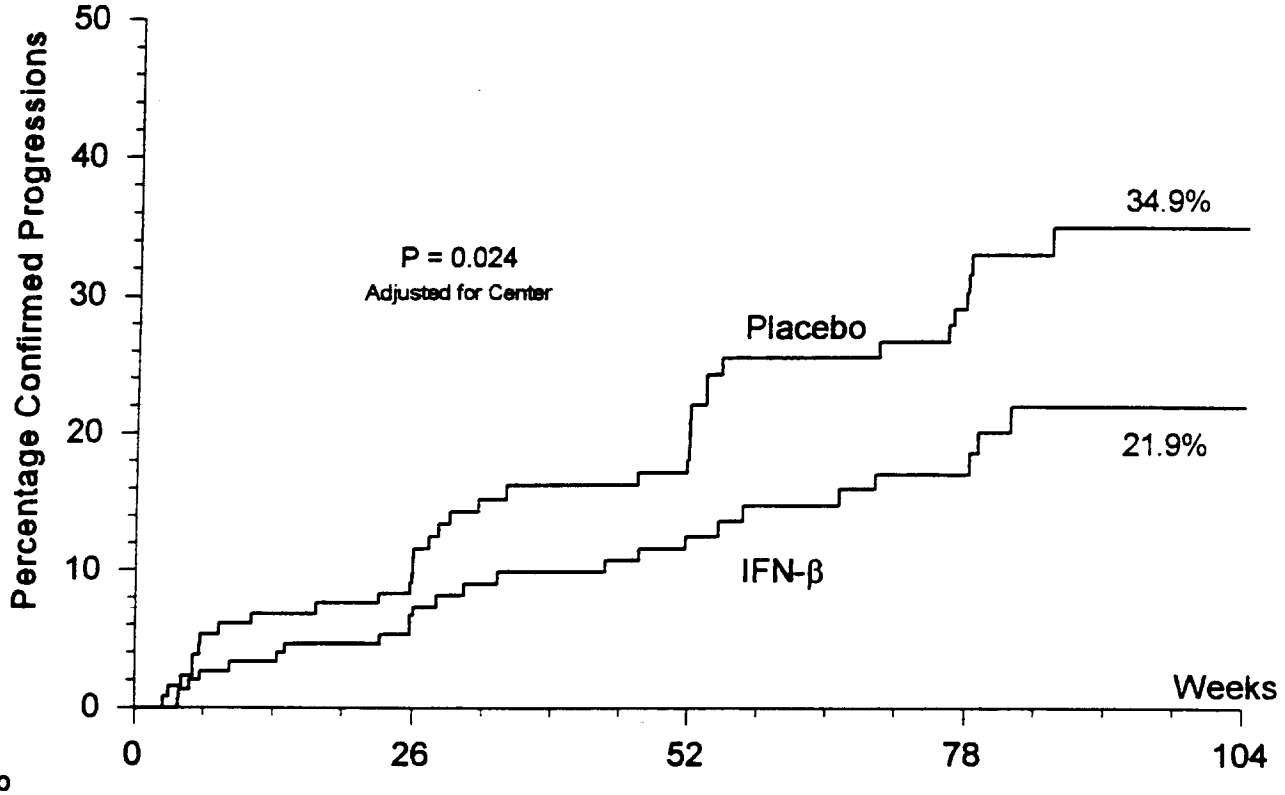
Evaluations for safety were at weeks 2, 4, 6, 8 and 12, and full evaluations for safety and efficacy occurred every six months. In addition, patients were instructed to call the study site whenever they suspected a worsening of the disease, and were asked to come to the study site for examination at that time. The intent-to-treat population, defined as all patients who were randomized, was to be used for all efficacy analyses. Amendments to the protocol decreased secondary efficacy endpoint assessments and analysis to 276 of the 301 patients, and terminated the study approximately 13 months early, in February 1994.

D. Pivotal Study Results for Efficacy

1. Primary Efficacy Endpoint

Although there were 301 patients enrolled in the study, 18 patients had less than 1 year on-study. These patients (11 placebo, 7 interferon) were censored at day 0. One of the excluded patients had a year on study, but the 52 week exam occurred after the prospectively defined cut-off date for inclusion. Two patients who dropped-out of the study earlier than 1 year on-study were included in the primary endpoint analysis by censoring at the 26 week exam, as defined by the rules of the analytic plan. Therefore, the primary endpoint includes 132 placebo patients and 151 interferon patients for time to confirmed progression. There were 60 confirmed progressions during the study; 36 in the placebo, 24 in the interferon group. The analysis was performed with Kaplan-Meier survival curves and the Mantel-Cox statistic with a log-rank test stratified by study site. These curves show a decrease in number of progressions in interferon group ($p=0.024$). The Kaplan-Meier curves estimating progression are contributed to by ever lessening numbers of patients as the study progressed, shown in the lower portion of the figure. A logistic regression

analysis was performed to examine if any of the demographic or baseline status parameters were important explanatory variables for the confirmed progression outcome. Study center was included in this analysis. Treatment assignment was the only parameter to significantly predict outcome.



Placebo

At risk at period start	143			109			80			49		28
Immediately censored	11			10			6			5		13
Censored during period		9			9			15			14	
Progressions during period		14			10			10			2	
Left at-risk at period end			109			80			49			28

rIFN-β

At risk at period start	158			136			94			62		25
Immediately censored	7			24			8			13		8
Censored during period		5			11			20			21	
Progressions during period		10			7			4			3	
Left at-risk at period end			136			94			62			25

The Kaplan-Meier curves estimate that the progression at the 2-year time is 21.9% in the

interferon and 34.9% in the placebo groups. Because 2 years is less than the median time to progress for both arms median time to progression was estimated from an exponential model. Estimated median progression times of 5.4 years for the interferon arm and 3.1 years for the placebo arm were calculated. With interferon treatment, 13% fewer of the treated patients would be expected to show progression after 2 years of treatment.

2. Secondary Efficacy Endpoints

Change in Disability at End of Study

In order to assess the amount of disability change to the end of study, the sponsor conducted an analysis using the confirmed change in disability from baseline to study-end for each patient. Confirmed change in EDSS was defined in a conservative manner using the last two available scheduled visits. For patients showing progression of EDSS at the last exams, the lesser progression EDSS was used. For patients showing improvement (reduction in EDSS) at the last two exams, the higher EDSS (lesser improvement) was used. There were 19 patients who had one EDSS higher and one lower than the baseline exam EDSS. The higher EDSS was used for these patients. There were 286 patients available for this analysis (150 interferon, 136 placebo). The mean confirmed change in EDSS were progressions in EDSS of 0.5 in the placebo patients and 0.2 in the interferon group (p=0.006, rank-sum test calculated with the individual changes).

Exacerbations & Steroid Usage

A: Time to First Exacerbation

Median time to first exacerbation on-study was 36.1 weeks for the placebo group, and 47.3 weeks for the interferon group (p=0.341, log-rank test, stratified by site). Exacerbation within the first three months on-study occurred nearly equally in both arms (26% placebo, 24% interferon).

B: Distribution of Exacerbations per Patient

The sponsor examined distribution of number of exacerbations per patient for year 1 of the study for patients with at least 1 year on-study, and for years 1-2 for patients with at least 2 years on study.

Although there was a modest trend to fewer exacerbations in the interferon group in the first-year-on-study data, there was no statistically significant difference between the groups. Approximately ⅓ each of the patients had none, one, or more than one (two or more) exacerbations during the first year on-study.

For the subset of patients with at least 2 years on study (85 interferon, 87 placebo) there were more with no exacerbations in the interferon group (38%) than the placebo group (26%), and fewer with more than one exacerbation (32%) than the placebo group (43%). This was statistically significant (p=0.027, Mann-Whitney rank sum test).

The sponsor suggested a lag time between initiation of treatment and onset of clinical benefit. Thus exacerbations are more appropriately assessed over a full 2 years. However, this analysis discards considerable patient on-study experience. The two-years-on-study analysis discards all patients who did not reach two full years on-study, i.e. all patients enrolled in the later portion of the study. An advantage of these analyses is an equality of patient weighting due to equal time contributed.

To address this, the data were reanalyzed in groups that still maintained the equality of patient followup time, but allowed an exploratory comparison of the effects of treatment. The data were divided into three subsets, each describing patient experience over a one-year period, with a full year of experience for each patient included (Table 2). The three subsets were:

- Year-1 information in patients who completed at least 1 year on-study, but did not complete 2-years. These were largely the later enrolled patients.
- Year-1 information in patients who completed at least 2 years on-study. These were the patients enrolled earlier in the study.
- Year-2 information in patients who completed at least 2 years on-study.

Table 2: Distribution of Exacerbations per Patient									
	1-Year Patient Subset			2-Year Patients during Year-1			2-Year Patients during Year2		
	Placebo	Interferon		Placebo	Interferon		Placebo	Interferon	
N, patients	45	65		87	85		87	85	
total number of exacerbations	36	67		88	61		68	46	
Exacerb. rate, annualized, per patient	0.80	1.03		1.01	0.72		0.78	0.54	
# of exacerb. per patient	**% of patients**		**p-value**	**% of patients**		**p-value**	**% of patients**		**p-value**
0	49	38		33	53		55	62	
1	31	32	0.664	43	31	0.112	21	28	0.096
2	13	23		16	9		17	15	
3	4	3		7	6		5	4	
4	2	2		0	1		2	0	
5 or 6	0	2		1	0		0	0	

comparison of all exacerbations in each treatment group using Mann-Whitney rank sum test

These analyses show that the patients who were on-study for at least two years derived benefit from interferon treatment in both year 1 and year 2 of their study period. However, the patients who were enrolled later in the study did not appear to derive benefit on number of exacerbations from their 1 year of study period. In fact their trend is toward more exacerbations on interferon. Approximately 20% of this subset of patients had 1 more exacerbation on-study than in the placebo group (alternatively, 10% had 2 extra exacerbations). This however, was not statistically significant.

There is no indication that benefit from interferon is delayed after treatment initiation. Rather, there may be a difference between the patients enrolled early and late in the study. However, this *post hoc* analysis is unable to provide definitive conclusions.

C: Percentage Exacerbation Free

The percentage exacerbation free was a prospectively defined endpoint. For the first-year-on-study subset, the trend to benefit with interferon did not reach statistical significance. The trend was stronger for the subset of patients with at least 2 years on-study (p=0.099 , Cochran-Mantel-Haenszel test).

D: Exacerbation Rate

Calculation of exacerbation rate on-study was not a prospectively defined endpoint, but was requested by CBER at the time of a pre-PLA meeting, due to the widespread use of this value for entry criteria or for an endpoint in MS clinical trials. The sponsor calculated this value as the group's exacerbation number per patient-year. That is, the total number of exacerbations per group for the period was divided by the total number of patient-years. The sponsor submitted this analysis on several subsets of patients, utilizing various portions of the on-study experience (Table 3).

Table 3: Annualized Exacerbation Rates

Study Portion	N Placebo; IFN	Placebo rate	Interferon rate	p-value	notes
First 3 months	142 ; 157	1.04	0.97	ns	
First year	132 ; 150	0.94	0.85	ns	
2 years	87 ; 85	0.90	0.61	0.002[1]	only 2-year completers
All On-Study Time	**(143 ; 158)**	**0.815**	**0.673**	**0.039**	
Post-injections	86 ; 83	0.73	0.52	ns	

[1]Comparison of treatment groups using likelihood ratio test

Patients who withdrew prior to reaching each of the designated time points were eliminated from the calculation. This may bias the result by elimination of patients who withdrew from disease progression and activity. The sponsor's analyses eliminate considerable patient experience from each calculation.

The CBER Statistical Review performed an alternative calculation that incorporates all available patient information. Using ratio estimation methodology, an estimate for the exacerbation rate that can accommodate varying amounts of followup time can be calculated and statistically tested. This is the method used in the analysis listed as "All On-Study Time" in Table 3. This analysis incorporates more of the patient experience than the sponsor's analyses. The result is quantitatively different, but not qualitatively. Interferon treatment still confers benefit to the patients.

E: Steroid Usage

A comparison of usage of steroid treatment courses (ACTH or methylprednisolone) between groups was a prospectively defined endpoint. The sponsor performed this analysis with study data subsets similar to that used for the exacerbation analyses (Table 4).

There was a mild trend to lesser steroid use in the year-1 only patient analysis which increased in effect size and reached statistical significance in the 2-year patient subset analysis.

Table 4: Steroid Treatment Courses

	Year 1 Patient Subset			Year 1&2 Patient Subset		
	Placebo	**Interferon**		**Placebo**	**Interferon**	
N	132	150		87	85	
total steroid courses	114	115		169	104	
Steroid use rate, annualized/patient	0.86	0.77		1.00	0.63	
# Steroid courses per patient	**% of patients**		**p-value**	**% of patients**		**p-value**
0	53	58		37	51	
1	23	25	0.295	20	27	0.010
2	14	9		14	8	
≥3	9	9		29	14	

Comparison of treatment groups using Mann-Whitney rank sum test

The frequency of steroid administration between groups was consistent with the frequency of exacerbations between groups.

Clinical-impression Exacerbations

All of the above analyses utilize the data on exacerbation as defined within the study. At each patient evaluation the Treating Physician determined, from clinical impression, if a clinical-exacerbation was occurring. If so, he/she also decided whether or not to administer a course of steroids. If a clinical-impression exacerbation was noted the patient was then seen by the Examining Physician to confirm or reject the exacerbation according to the protocol definition. There were numerous cases where a clinical exacerbation did not meet the criteria for a protocol-defined exacerbation.

When the superset of exacerbations defined as either clinical-impression or protocol-defined exacerbation is used, the annualized exacerbation rates are approximately ⅓ higher, but the treatment effect of benefit with interferon use remains (Table 5). The apparent decrease in exacerbations with interferon treatment is not an artifact of a restricted protocol-definition of exacerbation.

Table 5: Annualized Exacerbation Rate				
	Year 1 Patient Subset		**Year 1&2 Patient Subset**	
	Placebo	**Interferon**	**Placebo**	**Interferon**
N	132	150	87	85
Protocol-Defined Exacerbation	0.94	0.85	0.90	0.61
Clinical-Impression OR Protocol-Defined	1.18	1.08	1.22	0.86

Steroid courses were used 91 times in the absence of a protocol-defined exacerbation. Of these, 85 were in the setting of a clinical-impression exacerbation. These are not violations of the protocol, as there was no prospectively declared criteria for use of steroids. However, this highlights the restricted definition of protocol-defined exacerbation. Clinically important events occurred that were sufficient to warrant use of steroids, but yet did not qualify as a protocol-defined exacerbation.

MRI

MRI endpoints were threefold: The distribution of the number of gadolinium-enhancing lesions, the volume of the gadolinium-enhancing lesions, and the T2-weighted images lesion volume. All four of the gadolinium-enhancement measures showed statistically significant treatment effects in favor of the benefit of interferon (Table 6), while the T2 lesion volume showed statistically significant effects only at the year 1 analysis (Table 7).

Table 6: MRI Gadolinium Lesion Endpoints						
	Year 1 Patient Subset			2-Year Patient Subset		
	Placebo	Interferon		Placebo	Interferon	
N in time subset	132	150		87	85	
Number of Gadolinium-enhancing lesions per patient						
N in analysis	123	134	p-value	82	83	p-value
	% of patients			% of patients		
0	58	70	0.024[1]	57	71	0.051[1]
1	14	13		15	13	
2	10	7		15	7	
4	7	3		2	2	
≥4	11	7		11	6	
mean # lesions	1.6	1.0		1.6	0.8	
Volume of Gadolinium-enhancing lesions per patient, mm³						
N in analysis	123	134	p-value	82	82	p-value
	% of patients			% of patients		
0	58	70	0.020[1]	57	72	0.010[1]
1-100	20	16		22	20	
101-200	8	10		7	4	
201-500	8	1		6	2	
501-1000	5	2		6	0	
≥1000	1	1		1	2	
mean lesion vol.	96.5	70.0		122.4	74.1	

[1]Comparison of treatment groups with Mann-Whitney rank sum test

Differences between the number of patients in each time-on-study based subset and the number of scans in the analysis are due to MRI scans which were technically inadequate to analyze (2-5 for each group in each subset) or were not performed (year 1 gadolinium MRI only, 4 placebo, 12 interferon group).

Table 7: T2-weighted MRI Lesion Volume				
		Placebo	Interferon	p-value[1]
Baseline	N	130	140	
	Median Volume	7672	6214	0.143
Year 1	N	116	123	
	Median % change in volume	-3.3	-13.1	0.023
	Median baseline volume	8365	6478	
Year 2	N	83	81	
	Median % change in volume	-6.5	-13.2	0.355
	Median baseline volume	8510	5520	

[1]Comparison between arms using Mann-Whitney rank sum test

Other Secondary Endpoints

There were a large number of additional secondary endpoints using the limb functional data, the neuropsychological batteries, and the patient self-report questionnaires.

There were too few failure-to-perform events for the limb functional test to show a treatment effect when evaluated according to the prospective analytic plan. These evaluations were analyzed utilizing a time-to-event analysis, with the event defined *post hoc* as a specific amount of worsening from baseline. The amount of change selected as a worsening event for several of these tests was based on the statistical distribution of patients values at baseline, rather than based on clinical meaningfullness. These were analyzed for both time to first worsening, and time to sustained worsening. These numerous analyses failed to show statistically significant differences between arms except for the time to sustained progression in the 25 Foot Walk time.

The neuropsychologic batteries did not show differences in the treatment arms. The Beck Depression Index (BDI) was included in the self-report measure battery. The analysis of the BDI data is further discussed in the Safety section.

3. Serum Neutralizing Activity

Patients were tested for anti-Interferon beta-1a serum neutralizing activity at baseline and at weeks 8, 12, and at each 6-monthly evaluation. There were 37 / 156 (24%) interferon group

patients who developed a positive titer at least once during the study, with 23 / 156 patients (15%) testing positive at least twice during the study. In the placebo group 5 /142 patients tested positive during the study, none more than once, and all at low titers (< 30). Of the 37 interferon patients that did develop positive titers, 7 did so by week 26, 16 at the week 52 test, 11 at the week 78 test, and 3 not until week 104. Maximum titer levels were less than 30 in 13 of the 37 interferon patients, between 30 to 15 in 14 patients, and 10 patients were greater than 150. Sustained progression in disability occurred in 4 of 37 patients with neutralizing activity. This was not statistically different than 20 of 119 patients without serum neutralizing activity. Serum neutralizing activity did not appear to be associated with accelerated disability progression.

E. Results for Safety

1. Pivotal Study

Deaths / Treatment Discontinuation due to Adverse Events

There was one death during the study, in a patient in the interferon group at week 40 on-study. Death was attributed to pulmonary embolus and cardiac arrhythmia, and considered related to the pre-existing cardiac disease. An exacerbation of the pre-existing disease by interferon cannot be excluded. Early discontinuation of study treatment occurred in 9 of 143 (6.3%) placebo patients and in 14 of 158 (8.9%) interferon patients. Six of the interferon patients, and 1 of the placebo patients discontinued for reasons clearly related to adverse events. The one placebo patient adverse event was occurrence of panic attacks. For the interferon treated patients, one patient had an exacerbation of migraine headaches (with prior history of migraines), one postinjection bronchospasms (confirmed by controlled rechallenge tests), and one of mild persistent leukopenia (in the setting of a history of chronic intermittent mild leukopenia). There was also one patient with peripheral vascular disease requiring treatment, one with anxiety, one with progression of dementia, and one death. Other reasons for patients to choose treatment discontinuation included progressive activity of multiple sclerosis, patient decision to change to a proven therapy (including 5 changing to Betaseron). There were 5 patients for whom the only explanation given is "personal reasons" without any further details.

Frequent Treatment Emergent Signs, Symptoms & Clinical Laboratory Abnormalities

Common and typical side effects of interferon treatment were seen in this study. These included headache, flu-like syndrome, muscle ache, fever, asthenia, nausea, chills, diarrhea, and dizziness. None of these events were serious although many were graded severe. Although many of these same effects occur in MS patients at higher rates than in the general population, the interferon treated group had higher rates and greater numbers of patients with multiple reports of these adverse events.

Table 8
Signs and Symptoms Occurring in at Least 15% of Patients in Either Treatment Group

	Placebo	Interferon	P-Value[1]
No. of Patients Dosed	143	158	
No. of Patients with a Sign or Symptom	141 (99)	158 (100)	0.225
Sign or Symptom			
Headache	82 (57)	106 (67)	0.095
Flu-like symptoms	57 (40)	96 (61)	<0.001
Cold symptoms	79 (55)	87 (55)	1.000
Muscle ache	21 (15)	53 (34)	<0.001
Nausea	32 (22)	49 (31)	0.118
Upper respiratory tract inf.	40 (28)	49 (31)	0.614
Urinary tract infection	39 (27)	43 (27)	0.897
Pain	29 (20)	38 (24)	0.582
Fever	18 (13)	37 (23)	0.017
Chills	10 (7)	33 (21)	0.001
Asthenia	18 (13)	33 (21)	0.065
Sleep difficult	23 (16)	30 (19)	0.547
Sinusitis	24 (17)	28 (18)	0.879
Diarrhea	15 (10)	25 (16)	0.234
Back pain	35 (24)	25 (16)	0.082
Depression	21 (15)	24 (15)	1.000
Dizziness	18 (13)	23 (15)	0.737
Accidental injury	37 (26)	22 (14)	0.013
Rhinitis	24 (17)	14 (9)	0.055
Edema	21 (15)	11 (7)	0.039
Rash	21 (15)	10 (6)	0.022

NOTE: Numbers in parentheses are percentages.
[1] Comparison of treatment groups using Fisher's exact test.

Infection of any kind was reported more frequently in the interferon group (11%) than placebo (6%) (not significant). There was a diverse range infections, including GI and respiratory viral syndromes, skin infections and one sexual transmitted disease. There was no increase in any specific infection category in the interferon group compared to placebo.

Abnormalities in hematologic parameters were reported in 8% of interferon patients and 3% of placebo patients. There were no prospective guidelines for judging occurrence or severity, and the clinical significance of these anemia events is uncertain. Abnormal white blood count was reported by 3% of the interferon group and 2% of the placebo group. This included the one

patient who discontinued interferon treatment due to the reproducible mild persistent leukopenia that occurred in the setting of a history of intermittent mild leukopenia.

Liver enzyme abnormalities were not reported in excess numbers of patients in the interferon group compared to the placebo group.

Injection site reactions have been important in other settings. In this study, injection site reactions were reported by 4% of the interferon group (6 patients), 1% in placebo; injection site inflammation in 3% of the interferon group (5 patients) and none of the placebo. Injection site pain was reported by 9% of both groups, and there were no reports of injection site necrosis.

Herpes zoster was a reported event in 2% of the placebo (3 patients) and 3% of the interferon group (4 patients). Herpes simplex was reported in 1 placebo patient, and 3 interferon patients. Combined herpes reactivation patients thus were 7 interferon (4%) and 4 placebo (3%).

No excess of menstrual dysfunction or related abnormalities were reported in the interferon group. One patient was receiving interferon and became pregnant while on-study. Reevaluation 1 month after the initial positive pregnancy test (subsequently reconfirmed) revealed no signs of intrauterine pregnancy and a decreased β-HCG level. She subsequently reported normal menses. This may represent a spontaneous abortion event secondary to interferon administration.

Serious Adverse Events

Serious adverse events were reported in 20% of placebo (28 patients) and 24% of interferon patients (38). The largest single type of event was a MS exacerbation requiring hospitalization. After exclusion of these events, 10% of placebo (n=14) and 16% of interferon (n= 25) patients had at least one serious sign or symptom.

Most events were related to preexisting disorders or disorders with a low suspicion for a causality relationship with interferon. Seizures and neuropsychiatric disorders are the two primary serious adverse events of possible relationship to interferon administration.

Seizures occurred in 4 patients on study (3 were serious), all receiving interferon. All received anticonvulsant medication and continued on interferon treatment. MS patients have an increased incidence of seizures compared to normal subjects. It is difficult to determine if the interferon treatment caused the seizure, increased an underlying propensity to develop seizures, or was purely coincidental.

Depression & Suicidal Tendency

Depression and suicidal tendencies are reported adverse effects of interferons in clinical use, and were raised as concerns in the clinical trials with a different beta interferon. Depression is a not uncommon occurrence in multiple sclerosis, and any therapy that can exacerbate this propensity

has the potential to convey significant harm to these patients.

There were no completed suicides during this study. There was one attempted suicide, in a patient on the placebo arm. Serious adverse events of depression were reported in three patients during the study, 2 in the placebo group, and 1 in the interferon group. Depression as a reported adverse event occurred in 15% of the patients in both groups. Suicidal tendency as a reported adverse event occurred in 2 patients in the placebo group (1%), and 6 patients in the interferon group (4%). This threefold increase was not statistically significant. Only one of the suicidal tendency reports was classified as a serious adverse event, this in one of the interferon patients (the suicide attempt serious AE in the placebo patient was not co-listed as a suicidal tendency AE). No study treatment discontinuations occurred due to depression.

The Beck Depression Index (BDI) is a commonly used tool to assess depression in clinical populations, and was utilized in this study at the 6-monthly evaluations. A score of >18 was defined as the cut-off between not depressed (0-18) and depressed (>18). Median score in both groups was 8 at baseline, and generally 6 or 7 at each of the subsequent evaluations, without any statistically significant difference between groups. Excluding patients who had BDI scores >18 at baseline, 14 placebo (12%) and 11 interferon (9%) patients had BDI scores >18 at least once during the study.

Recognized antidepressant agents were utilized at least sometime during the study in 44% of the placebo group and 38% of the interferon group. Many of these agents are frequently used for non-depression purposes, and their use for this was balanced between the groups. In this study population other classes of medications, particularly benzodiazepines, were also used with the stated rationale of depression. 30% of placebo patients received a medication at least once during the study with a rationale at least partly consisting of depression, while this occurred for 23% of interferon patients. Note that both of these percentages are greater than the reported 15% incidence of depression in this study. There was no evidence of excess depression in the interferon group based on usage of concomitant medications .

2. Additional Safety Information

The Integrated Summary of Safety submitted by the sponsor combined safety analyses in the multiple sclerosis study with safety related information from Long-Term Dosing (LTD) and Short Term Dosing (STD) studies of Interferon beta-1a in other indications that have been investigated. Review of the adverse event information on 290 patients from these studies revealed no additional major safety concerns for MS patients. The most notable difference was a much higher incidence (52%) of injection site inflammation and pain in the LTD study patients. Injection site necrosis was also an observed event in 3/231 patients in the LTD studies. The increased incidence of injection site inflammation and the observation of injection site necrosis in the LTD studies is probably due to differences in the dosing regimen which included the use of higher dosages, greater frequency of injections, and injection by the subcutaneous route as opposed to the intramuscular route used in MS patients.

Safety data is being collected in an open-label, extension study of relapsing MS using BG9418 (Interferon beta-1a produced at commercial scale). The results of an updated interim safety report submitted March 15, 1996 indicate that most adverse events are of mild or moderate severity and of a frequency similar to that seen in the pivotal trial. No injection site necrosis was reported. The serious adverse event cut-off includes data on 380 patients, while the standard adverse event cut-off includes data from 274 patients. A total of 24 serious adverse events were reported in 16 patients and include: 12 MS exacerbations; 3 reports of depression; and 1 each of cellulitis, thrombophlebitis, gastroenteritis, GE reflux, bowel impaction, seizure, sepsis, uterine disorder, and asthenia.

Of 274 full reporting patients:

Amount of Exposure	
Duration of Exposure (weeks)	N
1 to < 4	3
4 to < 8	18
8 to < 13	38
13 to < 26	116
26 to 29	99
Median weeks	15
Mean Weeks	18

F. Pivotal Study Summary

- The pivotal study was a randomized, double-blind, placebo controlled multicenter study designed to assess the efficacy and safety of 30µg IM q-week Interferon beta-1a in multiple sclerosis patients with a relapsing component to their disease.

- The primary endpoint was progression of disability, as measured by a 1.0 change in Kurtzke Expanded Disability Status Score (EDSS), sustained for at least 6 months to lessen effects of variability from disease fluctuation and intrarater variability.

- Secondary endpoints were numerous. They included comparisons of the number of

exacerbations and effects on magnetic resonance imaging (MRI).

- The initial design was a four year trial of 312 patients with two years of treatment and 2 to 4 years of evaluations in all patients. This was changed to a trial of 301 patients with 11 months to 2 years of treatment, and 11 months to 3¼ years of evaluations.

- The study population consisted of patients who were in either relapsing-remitting or relapsing-progressive categories of MS, with mild to moderate impairments (EDSS of 1.0 to 3.5).

- The two treatment groups are well balanced for demographics and baseline disease status parameters.

- Based on the patients with non-zero time at-risk, the primary endpoint of time to progression in EDSS was lengthened by treatment with interferon ($p=0.024$), with estimated progression at 2 years of 35% placebo, 22% interferon. These results were consistent at three of the four sites.

- The distribution of number of exacerbations per patient improved with interferon treatment in the subset of patients on-study for at least two years, but was not significant when analyzed using the larger number of patients on-study for at least 1 year.

- Exacerbation rates per year per patient were similar. They were statistically different for the 2-year patient subset, but not for the 1-year patient subset. When all patient on-study time was analyzed there was a treatment effect.

- MRI gadolinium-enhancing lesions showed a significant decrease in both number and volume at both the end of year 1 and end of year 2 scans.

- MRI T2 lesion volume showed statistically different effects at the end of year 1 but not year 2 scans.

- Treatment discontinuation occurred in 14 interferon patients. None were for serious adverse events except for the one death on-study. The death was attributed to pre-existing cardiac disease, but an interferon related exacerbation of the pre-existing disease cannot be excluded.

- There was no evidence of increased depression with interferon treatment based on adverse event reports, concomitant medication usage, or the Beck Depression Index.

- The common and typical side effects associated with interferon treatment were frequently seen in this study. There were many with grades of severe, but no event was classified as serious.

VI. CLINICAL SUPERIORITY

Under the regulations of the Orphan Drug Act, Biogen's Interferon beta-1a was determined to be a different product from Chiron's Interferon beta-1b, because of a difference in safety profile involving the occurrence of injection site skin necrosis with the Chiron product, but not the Biogen product. Analyses of the safety data submitted in the Biogen PLA showed that no injection site necrosis was reported in the 158 patients treated with Interferon beta-1a in the phase 3 study (0%). In contrast, the incidence of injection site necrosis reported in Chiron's PLA was 5% in the 124 patients treated with Interferon beta-1b in the phase 3 study. Further supportive evidence for a difference in skin necrosis incidence is suggested by the 85% incidence of injection site reactions in the Chiron phase 3 study versus only 4% in the Biogen phase 3 trial.

Biogen is also conducting an open label safety study of Interferon beta-1a (BG9418) in MS. The study uses the same dose and regimen proposed for licensure and shows that in 274 patients treated for 1 to 29 weeks there were no reports of injection site necrosis and only 4 patients (1%) who reported an injection site reaction. Thus the safety profile of BG9418 is consistent with that seen for the BG9015 product used in the pivotal trial, and continues to show a better safety profile than Chiron's Interferon beta-1b with regard to the injection site skin necrosis.

VII. ADVISORY COMMITTEE RECOMMENDATION

Data regarding the manufacture, safety, and efficacy of Interferon beta-1a were discussed at the Peripheral and Central Nervous System Drugs Advisory Committee on December 4, 1995. The committee concluded that the product was safe and effective for the treatment of relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. The committee noted that the results of the study did not extrapolate to patients with largely progressive characteristics to their disease (secondary chronic progressive and/or primary progressive patients).

VIII. PHASE IV COMMITMENTS

As a condition of approval, Biogen was asked to perform the following phase IV clinical studies:

1. A randomized, double-blind placebo controlled study in chronic progressive multiple sclerosis using disability as a primary endpoint, to determine efficacy and safety of Interferon beta-1a treatment in this patient population.

2. A randomized, controlled study to assess the dose efficacy response relationship of Interferon beta-1a treatment in multiple sclerosis.

3. A randomized, controlled study to assess the usefulness of continued treatment with Interferon beta-1a beyond two years.

4. MRI assessments and examination of the strengths and weaknesses of MRI as a surrogate for clinical outcomes, evaluations to determine the extent of depression or aggravation of pre-existing psychiatric disease with Interferon beta-1a treatment, and evaluations of antibody formation against Interferon beta-1a, and assessment of possible clinical correlations with effectiveness when antibodies are developed.

1X. APPROVED PACKAGE INSERT

A copy of the approved package insert is attached.

SIGNATURES OF LICENSING COMMITTEE

David Finbloom, M.D. Chairman

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